



The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

SEP 07 2016

Dear Mr. Chairman:

Thank you for your March 29, 2016, letter regarding the public health response to the Zika virus. Enclosed are responses to the questions you posed in your letter.

I hope this information is helpful to you. Thank you for your continued commitment to public health preparedness.

Sincerely,

A handwritten signature in black ink, reading "Jim R. Esquea". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Jim R. Esquea
Assistant Secretary for Legislation

cc: The Honorable Frank Pallone, Jr.
Ranking Member

Enclosure

Enclosure

1. Who has been designated as the lead Federal official for the Federal government's response to the Zika virus, pursuant to the Pandemic and All Hazards Preparedness Act (PAHPA)?

The White House is managing the interagency coordination on Zika preparedness and response, for which the Department of Health and Human Services (HHS) is the lead federal agency domestically. HHS continues to manage its day-to-day efforts through its Operating and Staff Divisions. For example, Dr. Nicole Lurie, HHS's Assistant Secretary for Preparedness and Response, is leading the Office of the Assistant Secretary for Preparedness and Response's (ASPR) efforts, Dr. Tom Frieden, Director of the Centers for Disease Control and Prevention (CDC), is leading CDC's efforts, Dr. Anthony S. Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID), is leading efforts within the National Institutes of Health (NIH), and Dr. Luciana Borio, the Food and Drug Administration's (FDA) Acting Chief Scientist, is leading efforts within FDA. Within HHS, ASPR activated the Disaster Leadership Group, HHS's primary coordinating body for preparedness, response, and recovery, on January 5, 2016, to make critical policy decisions and identify potential barriers to a response. ASPR took this step, consistent with its authorities under the Pandemic and All Hazards Preparedness Reauthorization Act.

2. There are currently no commercially available diagnostic tests for Zika virus. How is the Department working with other Public Health Emergency Medical Countermeasures Enterprise partners to ensure public-private partnerships and incentivize private companies to produce medical countermeasures (MCM), including diagnostics, vaccines, and therapeutics, against Zika?

Since your letter dated March 29, the Food and Drug Administration (FDA) has authorized the use of eight commercially available diagnostic tests for Zika virus under its Emergency Use Authorization (EUA) authority:

- On April 28, FDA authorized the emergency use of Quest/Focus Diagnostics, Inc.'s Zika virus ribonucleic acid (RNA) qualitative real-time reverse transcription polymerase chain reaction test. This test is able to detect Zika virus in the blood of patients who have Zika virus, and is indicated for patients with symptoms who might have been exposed to Zika virus because, for example, they live in, or have traveled to, an area with ongoing Zika virus transmission. This was the first commercial test to detect Zika virus authorized by FDA for emergency use.
- On May 13, FDA authorized the emergency use of a second commercial test, Altona Diagnostics RealStar Zika Virus RT-PCR Kit U.S., to detect Zika virus in the blood or urine of patients who have symptoms of Zika virus infection and live in or have traveled to an area with active Zika virus transmission.
- On June 17, FDA authorized the emergency use of Hologic, Inc.'s fully automated Aptima Zika Virus Assay to detect Zika virus in the blood of people who have symptoms

of Zika virus infection and live in or have traveled to an area with active Zika virus transmission.

- On July 19, FDA authorized the emergency use of Viracor-IBT Laboratories, Inc.'s ("Viracor-IBT") Zika Virus Real-time RT-PCR test for the qualitative detection of RNA from Zika virus in human serum, plasma or urine from individuals meeting CDC Zika virus clinical criteria.
- On July 29, FDA authorized the emergency use of the Siemens Healthcare Diagnostics Inc.'s VERSANT® Zika RNA 1.0 Assay (kPCR) Kit for the qualitative detection of RNA from Zika virus in human serum, EDTA plasma, and urine from individuals meeting Zika virus clinical criteria.
- On August 4, FDA issued a EUA to authorize the emergency use of Luminex Corporation's xMAP® MultiFLEX™ Zika RNA Assay for the qualitative detection of RNA from Zika virus in human serum, plasma, and urine.
- On August 17, FDA issued a EUA for emergency use of InBios International, Inc.'s ZIKV Detect™ IgM Capture ELISA for the presumptive detection of Zika virus IgM antibodies in human sera.
- On August 26, FDA issued a EUA for emergency use of Roche Molecular Systems, Inc.'s LightMix® Zika rRT-PCR Test for the qualitative detection of RNA from Zika virus in human serum and EDTA plasma.

These tests are only authorized for use by laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 to perform high-complexity tests, or by similarly qualified non-U.S. laboratories.

ASPR has coordinated with Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) partners at the CDC, NIH, FDA, and Department of Defense (DOD) to develop a strategy for developing medical countermeasures (MCM) for Zika virus that prioritizes the development of vaccines, diagnostics, and donor blood screening tests and pathogen reduction technologies to protect the blood supply. FDA is fully engaged with partners across the federal government and with the private sector to facilitate the development and availability of MCMs for Zika virus including vaccines and diagnostic tests as well as donor blood screening tests and pathogen reduction technologies to protect the blood supply.

The Biomedical Advanced Research and Development Authority (BARDA), a component of ASPR, and NIAID both have open funding opportunities posted. NIAID's funding opportunity focuses on basic research and early development of improved or novel technologies and platforms, while BARDA's focuses on advanced development. BARDA has responded to expressions of interest from industry by hosting a number of Zika-focused Tech Watch meetings on topics ranging from the development of diagnostics and vaccines to the development of pathogen reduction technologies and insect repellents. NIH/NIAID, ASPR/BARDA, CDC, and FDA also co-sponsored a stakeholders' workshop on Zika virus MCMs to identify the current

status of MCM development for Zika virus as well as to identify gaps and research priorities to accelerate MCM development for Zika virus. Over 700 participants registered for the onsite workshop, and an additional 400 people participated by webcast and telephone. The workshop included participation from representatives from the federal government, academia, industry (large pharmaceutical and biotechnology companies), multilateral health agencies, and the Brazilian government and industry.

Under its innovations Broad Agency Announcement (BAA), BARDA has received a number of proposals to develop new Zika virus vaccines using vaccine platforms that could also be used for other emerging infectious disease threats, and pending the availability of funding, anticipates establishing public-private partnerships to support such efforts. ASPR/BARDA is also providing funding and technical assistance to the Butantan Institute, a long-time partner in Sao Paulo, Brazil, to support the development of a whole virion inactivated Zika virus vaccine. Finally, ASPR/BARDA, NIH, and DOD are collaborating to support the development of a whole virion inactivated vaccine at DOD's Walter Reed Army Institute of Research (WRAIR). Small scale manufacturing and preclinical evaluation are currently proceeding at WRAIR, and NIH's NIAID is supporting safety evaluation studies in animals. Current plans are for the vaccine to be tested in Phase I trials this fall through NIAID's Vaccine and Treatment Evaluation Units and WRAIR. BARDA anticipates transferring this vaccine technology to one of the HHS Centers for Innovation in Advanced Development and Manufacturing (CIADM) for process optimization and larger scale manufacturing. Potential industry partners have already approached the federal government and expressed interest in out-licensing this candidate vaccine. If such a public-private partnership can be established, it would represent a highly significant development and a great accomplishment for federal government collaboration.

HHS interagency partners have defined five main strategic goals for Zika virus diagnostics. These goals are to: 1) expand Zika virus molecular and serological diagnostics testing capacity in the Laboratory Response Network (LRN), an integrated network of state and local public health, federal, military, and international laboratories, as well as in commercial laboratories for acute infections and previous Zika infections, especially for pregnant women; 2) advance the development of additional commercial molecular and serologic assays for use in the United States (U.S.) and elsewhere; 3) identify, collect, produce, and distribute necessary development reagents and materials including viruses, antigens, clinical samples and reference panels for test validation; 4) develop, validate, and implement the use of high-throughput molecular detection assays to detect Zika virus in the blood supply; and 5) define and communicate to developers the FDA regulatory pathways for development, approval or clearance, and emergency use of Zika virus diagnostic tests. Specific activities to date in support of these goals include:

- Efforts to obtain samples (e.g., blood to advance diagnostic and MCM development) from individuals confirmed to have Zika virus infection both domestically and internationally in collaboration/partnership with Panama, state and local health departments, contract research organizations, and existing clinical networks and investigators;
- Engagement with industry to produce antigens and antibodies for use in diagnostic test development and test controls;

- Modification of open ASPR/BARDA and NIH/NIAID funding solicitations to include funding opportunities for Zika diagnostics. The amendment includes development of point-of-care and laboratory-based serologic assays for Zika virus, and multi-analyte assays to distinguish between Zika, dengue, and chikungunya virus infections; and
- Engagement with diagnostic test developers interested in developing diagnostic tests for Zika virus to help accelerate development programs, including providing templates that delineate data requirements for the authorization of the use of Zika diagnostic tests under FDA's EUA authority.

To protect the blood supply, ASPR/BARDA is interested in supporting the late-stage development of pathogen reduction systems for blood products that may be contaminated with Zika virus. The successful development of such systems would minimize concerns about the contamination of the blood supply by Zika and other emerging infectious diseases.

ASPR/BARDA is also planning to support at least one industry partner in the development of a high through-put screening system for detection of Zika virus in blood using existing molecular technologies. This will allow for the rapid screening of donated blood products, thereby preventing the need to halt blood collection in areas, such as Puerto Rico, with ongoing Zika transmission.

3. Please provide a detailed description of the three diagnostic tests used for the Zika virus. As a part of your response, please include information on:

a. The procedures and amount of time necessary to complete each test:

There are three types of diagnostic tests needed for Zika virus: 1) a test to diagnose acute infection; 2) a test to assess whether individuals who were potentially exposed to Zika virus were actually infected; and 3) a test to confirm positive or equivocal serological (IgM) results. There are currently ten diagnostic tests for Zika virus authorized for emergency use under FDA's EUA authority, including both CDC-developed tests and private sector-developed tests. Eight of the tests diagnose acute infection and two of the tests are to assess whether individuals who were potentially exposed to Zika virus were actually infected.

To determine the presence of Zika virus within two weeks of infection, the CDC-developed molecular (RT-PCR) test measures Zika genetic material in blood or urine. For blood, the PCR tests simultaneously for Zika, dengue, and chikungunya viruses. This is the most specific Zika diagnostic available – a positive test means the patient has recent Zika infection. However, not all patients with Zika infection will have positive test results, and positivity fades in a few days from blood and in 1-2 weeks from urine. The RT-PCR test takes approximately four hours to perform. There are also seven commercial PCR tests approved for emergency use by FDA.

The CDC's Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA) and the commercial InBios International, Inc.'s ZIKV Detect™ Capture ELISA assess whether individuals who were potentially exposed to Zika virus are actually infected. These tests can be used to detect recent Zika virus exposure up to 8-12 weeks post infection. The Zika

MAC-ELISA takes approximately three days to complete whereas the commercial ZIKV Detect™ IgM Capture ELISA, which comes with pre-coated IgM capture ELISA plates, takes less than 1 day. Additionally, both tests cannot completely discriminate between Zika and some related viruses, so positive or equivocal results for the Zika MAC-ELISA and presumptive and possible Zika positive for the ZIKV Detect™ IgM Capture ELISA require confirmation following the latest CDC guidelines that can include plaque-reduction neutralization test, or PRNT.

Another tool, the PRNT is currently used as a confirmatory test for positive or equivocal Zika MAC-ELISA test results. PRNT is not used as an initial test for Zika virus because it is complex and specialized, taking 7 to 10 days for results. The test is being used in CDC and New York State laboratories. NIAID investigators and grantees are currently developing alternative Zika neutralization tests that are specific for Zika and are potentially simpler and more rapid to perform than the PRNT test.

Building on experience applying advanced molecular detection technology to address the emergence of chikungunya virus, CDC scientists were able to develop and validate a Zika test protocol for use in laboratories throughout the Western Hemisphere within three weeks of having received the first Zika virus-positive sample. With older methods, this would have required three to four months.

b. The current overall capacity to test for the Zika virus in the United States, including U.S. territories:

The CDC laboratory in Fort Collins receives a high volume of tests from throughout the United States. For maximum efficiency, the laboratory separates tests from people with reported symptomatic illness from those with no reported symptoms then processes the tests in the order in which they were received. The CDC laboratory in Puerto Rico (San Juan) primarily receives tests from Puerto Rico. Due to the Zika outbreak in Puerto Rico, this laboratory prioritizes tests based on pregnancy status and other factors. CDC Fort Collins can perform 800-1000 rRT-PCR tests, 1400 Zika MAC-ELISA tests, and 600 PRNT tests per week. CDC San Juan can perform 4500 rRT-PCR tests and 1500 Zika MAC ELISA tests per week.

Additional testing capacity for CDC's rRT-PCR and MAC-ELISA tests is available through the LRN, an integrated network of domestic and international laboratories that can respond to biological and chemical terrorism, and other public health emergencies and are able to perform testing to detect and report cases. On the biological side of the LRN, there are currently more than 150 member laboratories, representing all 50 states, as well as international locations.

Three commercial laboratories are also proficient in the CDC Zika IgM ELISA: Quest Diagnostics, LabCorp, and Mayo Medical Laboratories.

As of August 26, 43 states plus the District of Columbia and Puerto Rico, and 8 DOD laboratories have received reagents for Zika MAC-ELISA, and 41 states plus the District of Columbia and Puerto Rico, and 4 DOD labs have completed the verification panel.

As of August 26, all states plus the District of Columbia and Puerto Rico and 16 DOD labs have received the Trioplex RT-PCR assay reagents and 48 states plus the District of Columbia and Puerto Rico and 16 DOD labs have completed the verification panel. Numbers of tests that can be performed per laboratory per week vary based on number of staff, available instrumentation, and resources.

c. How the Department plans to increase this capacity in the coming months, particularly as we approach the season when local transmission of Zika in the United States becomes more likely:

CDC is facilitating testing for Zika virus and working to distribute test kits to qualified laboratories in the LRN. CDC is building laboratory capacity and infrastructure to test for Zika virus and other infectious diseases across the United States by providing critical laboratory supplies, reagents, equipment, and training for diagnostic testing and surveillance activities in states and territories. CDC resources are supporting laboratory surge capacity, which will help meet state testing needs, especially in Puerto Rico. In addition, CDC continues to work on improving diagnostics for Zika.

d. Whether the capacity for diagnostic testing is sufficient to meet levels of demand, particularly among pregnant women:

As of September 1, there is no CDC backlog on testing for Zika virus. CDC has expanded capacity at its laboratories, and has equipped LRN laboratories around the country to conduct testing locally. In preparation for a possible increase in demand, a CDC laboratory based in Atlanta has been trained and equipped to accept specimens for MAC-ELISA testing. If CDC detects a further increase in demand, it can expand capacity through training of additional staff at CDC and within state and local health departments via the LRN. CDC also partners closely with the Association of Public Health Laboratories, or APHL, which can also assist with expansion of laboratory capacity. FDA has issued eight EUAs for commercial diagnostic tests and continues to work with diagnostic developers to make additional diagnostic test available as quickly as possible. Further, availability of commercially manufactured tests would also assist with capacity.

e. How many CDC staff are currently trained and performing PRNT tests for the Zika virus:

Currently, there are six staff in the CDC Fort Collins laboratory capable of performing the PRNT test for Zika virus and four to eight more staff are to be trained in Fort Collins and Puerto Rico. California and New York State Department of Health laboratories also perform PRNT, with New York State Department of Health also supporting PRNT for New Jersey. The CDC laboratory in Atlanta has recently established the PRNT and will soon begin performing the test. Presently, there are plans to build CDC surge capacity for PRNT outside of the CDC Fort Collins laboratory.

4. What is the current status of research into more advanced diagnostic testing for the Zika virus, not discussed above, and what hurdles impair the creation of faster and more accurate diagnostic tests for the Zika virus. Please provide a description of any research undertaken or funded by the Department.

The availability of sufficient volumes of Zika positive blood from infected individuals remains one of the major obstacles to development and regulatory approval of new diagnostic tests for Zika infection. As described above, efforts are underway to collect blood from volunteer donors in the U.S., Puerto Rico, and other affected countries. This effort requires many steps, including collaboration of state and local health departments and affected country Ministries of Health to identify both the donors and sites for the blood collection. Newly collected blood specimens must be re-analyzed by the CDC to assess their suitability for test development.

A diagnostic challenge is that Zika virus is present in blood for a only approximately the first five to seven days after infection (from the mosquito bite) and present in urine for approximately 14 days after onset of symptoms. Zika virus rRT-PCR should be performed on urine collected less than 14 days after onset of symptoms in patients. However, as viremia decreases over time, a negative RT-PCR collected after symptom onset does not preclude Zika virus infection. Another major hurdle in the development of new diagnostics is that many of the antibodies produced to flavivirus infections such as dengue and Zika viruses are cross-reactive, meaning it is difficult for a test to discriminate between these two infections, a positive result for Zika may actually be a “false positive” due to a prior dengue infection. This is especially problematic in making a diagnosis for individuals previously exposed to dengue or other flaviviruses, and additional testing to characterize neutralizing antibodies is required. This test is complex and is therefore only available at CDC Fort Collins, California and New York State Department of Health laboratories. Efforts to try to resolve the cross-reactivity have been attempted by flavivirus researchers for many years without success. New research efforts supported by NIH and ASPR/BARDA include work to utilize new technologies to create new antigens that can be used in diagnostic tests to reduce this cross-reactivity without reducing the sensitivity of the test. Specifically, NIAID is working to address cross-reactivity between Zika virus and dengue virus, the key challenge faced by the current serologic tests. NIAID grantees are working to generate antibodies that can distinguish between Zika virus and dengue virus. These Zika-specific antibodies potentially could be used to develop antibody-based tests for Zika virus that do not cross react with dengue virus.

Efforts are also underway to develop rapid and sensitive tests that can be used at the point of care to detect Zika virus antibodies. While the technology exists to create these tests, and several companies have tests in development, the problem of cross-reactivity limits their utility plus rapid tests are typically not as sensitive as laboratory tests. ASPR/BARDA has awarded development contracts to Chembio Diagnostic Systems and Orasure technologies to develop rapid point of care diagnostics to detect Zika virus antibodies. It is believed that these two companies will be able to overcome the obstacles to developing rapid Zika serology tests. NIH and BARDA are engaging with researchers to develop new reagents that may resolve this challenge to reliable, rapid diagnostic tests for Zika virus. Finally, NIAID is supporting efforts to validate a new diagnostic and sequencing method, VirCapSeq-vert, a technology that would

enable simultaneous testing for many different viruses and provide near-complete sequences of their genomes.

5. Please provide a description of current research undertaken by or funded by the Department in the following:

a. Any potential vaccines for the Zika virus:

NIAID is investigating multiple Zika virus vaccine candidates, including several based on platforms used against other flaviviruses. NIAID Vaccine Research Center (VRC) scientists are developing a DNA-based Zika virus vaccine that is similar to a West Nile virus vaccine previously developed by NIAID. The West Nile virus vaccine candidate was shown to be safe and to generate a strong immune response in a Phase I clinical trial, indicating that this platform may be useful for Zika vaccine development. On August 3, NIAID announced the start of a Phase I clinical trial of the DNA-based Zika virus vaccine. This trial will examine the experimental vaccine's safety and ability to generate an immune system response in at least 80 healthy volunteers at three study sites in the United States, including the NIH Clinical Center in Bethesda, Maryland. In addition to the DNA-based Zika virus vaccine, VRC scientists are planning to develop an mRNA vaccine targeting the membrane and envelope proteins of Zika virus. Basic research regarding this approach is currently underway and builds on the DNA vaccine development work. NIAID researchers in the Laboratory of Infectious Diseases are also developing a live-attenuated Zika virus vaccine candidate. This effort employs a similar strategy to that used by NIAID to develop a vaccine against dengue virus. The dengue vaccine candidate was shown to be safe and to generate strong immune responses in early-phase clinical trials, and it is currently being evaluated in a large Phase III clinical trial in Brazil. NIAID also is supporting the development of several additional Zika vaccine approaches, including an early-stage vaccine candidate based on recombinant vesicular stomatitis virus, the same virus used successfully to create an investigational Ebola vaccine that has been tested in West Africa.

There is collaboration between HHS (NIH/NIAID and ASPR/BARDA) and DOD (Walter Reed Army Institute of Research – WRAIR) to make an inactivated whole virion vaccine. Preclinical testing of the vaccine candidate is currently ongoing with human clinical studies supported by NIH/NIAID and WRAIR to start in the fall. BARDA anticipates transferring the WRAIR vaccine candidate to one of the HHS Centers for Innovation in Advanced Development and Manufacturing (CIADM) for process optimization and larger scale manufacturing. This vaccine candidate will also be eligible for out-licensure to industry partners and some discussions with potential partners have already begun.

Further, ASPR/BARDA is collaborating with the Butantan Institute in Sao Paulo, Brazil to assist them in developing their own inactivated virus Zika vaccine. ASPR/BARDA sent technical subject matter experts in mid-April to review Butantan's facilities, development plans, and timeline, and to provide needed technical assistance. BARDA is working closely with the WHO to make funds available to Butantan to accelerate this effort to be able to respond locally to the current Zika virus outbreak.

ASPR/BARDA is also continuously assessing the landscape of vaccine development efforts by large pharmaceutical and small biotech companies and, to date, has identified close to 30 candidate vaccines under development for Zika virus. Almost all of these are in the early discovery stage and at least five distinct approaches to vaccine development are being pursued. Three companies are in the pre-clinical evaluation stage with data expected sometime in late spring or early summer with human clinical studies tentatively scheduled to start in late 2016 or early 2017. ASPR/BARDA has informed these companies of the opportunity to present their technologies to the U.S. Government through the Tech Watch program and of funding opportunities through BARDA's Broad Agency Announcement and NIAID announcements.

b. Any potential therapeutics for the Zika virus:

NIAID also has an active program to screen for antiviral drugs active against viruses in the flavivirus family, including dengue, West Nile, and yellow fever viruses. Building on these efforts, NIAID has developed an assay to test compounds, antibodies, or peptides for antiviral activity against Zika virus. So far, 230 tests have been run in the primary assay, of those, 26 tests yielded high to moderate activity. NIAID also is working with NIH's National Center for Advancing Translational Sciences (NCATS) to use this assay to screen a library of approved drugs for activity against Zika virus.

NIAID-supported scientists also have developed a rodent animal model for Zika virus infection to evaluate the efficacy of promising antiviral compounds. In a recent NIAID-supported study, BCX4430, a broad-spectrum antiviral drug originally developed as a candidate therapeutic for Ebola and Marburg viruses, in collaboration with its developer BioCryst, was found to protect immune-deficient mice infected with Zika virus. One goal of NIAID-supported therapeutic research is to develop a broad-spectrum antiviral drug that could be used against a variety of flaviviruses, including Zika. Finally, NIAID is supporting identification of monoclonal antibodies which could be used as therapeutics or for prevention of Zika virus infection.

c. The link between Zika virus infection and microcephaly or other birth defects in infants:

On April 13, CDC concluded that Zika virus can be a cause of microcephaly and other severe fetal brain defects. The causes of microcephaly are multiple and vary in outcomes. Causes can include genetic, syndromic (such as Rett syndrome), environmental (e.g. lead poisoning), metabolic (PKU, which is detected through newborn screening), and teratogenic (fetal alcohol syndrome, or neurotropic viruses such as cytomegalovirus [CMV], and rubella.) Microcephaly and its effect on function can vary among individuals, depending on its cause and the extent of brain malformation and damage. To date, research on the causes of microcephaly have been conducted largely in animal models, testing possible therapies to treat inflammation that results in brain damage. Other research is exploring different methods of screening for perinatal brain injury, which may be especially useful in settings where MRI is not feasible.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NIAID, the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Environmental Health Sciences (NIEHS), all components of the NIH, have active research underway looking at Zika virus infection and microcephaly or other severe fetal

brain defects. These efforts aim to establish the pathogenesis driving congenital anomalies, the risks posed by infection with the Zika virus at different stages of pregnancy, the potential health outcomes for babies born to Zika-infected but asymptomatic women, and how to best evaluate and manage the health of children exposed to Zika virus in utero. To address the health needs of these children, NICHD is planning a scientific workshop for September 2016 that will develop a plan to fill the gaps in our knowledge.

NICHD, NIAID, NIEHS, and the Foundation Oswaldo Cruz in Brazil (Fiocruz) are leveraging existing research programs in Latin America on CMV and other infections to study the link between Zika infection and congenital disease outcomes in pregnant women and their babies. This study (Zika in Infants and Pregnancy or ZIP study) is a multi-center, international, prospective study of up to 10,000 women who will be enrolled during their first trimester of pregnancy and will be followed (along with their infants) for up to two years. The inclusion of environmental measures, as well as socio-economic status and nutrition and folate intake into the research protocols are being discussed by the NIH and ZIP researchers.

NIAID is currently supporting natural history studies of Zika to further characterize the clinical outcome in babies born to symptomatic pregnant women in Brazil. NINDS intramural researchers are developing animal models and in vitro systems to study the pathophysiology of microcephaly and Guillain-Barré syndrome associated with Zika virus. NINDS supplemented an ongoing grant that is studying how the unique stem cells (or *progenitor* cells) in the developing human cerebral cortex give rise to the mature cortex. The administrative supplement will investigate the mechanisms by which the Zika virus disrupts normal human cerebral cortical development to cause microcephaly. These researchers have already published initial results (Nowakowski et al. Cell Stem Cell 2016 Mar 28). Another team of researchers with NINDS grants to study normal brain development were able to quickly start studying the effects of Zika on those neural development processes and have already published their findings (Tang, et al. Cell Stem Cell 2016 Mar 4).

To further stimulate Zika-specific research, several NIH Institutes have issued notices to alert the research community about NIH's interest in supporting grants in this area. High-priority research areas include assessing the impact of infection during pregnancy. These notices may be accessed by going to: <http://grants.nih.gov/grants/guide/pa-files/PAR-16-106.html>, <http://grants.nih.gov/grants/guide/notice-files/NOT-HD-16-004.html>, <https://grants.nih.gov/grants/guide/notice-files/NOT-HL-16-307.html>, and <http://grants.nih.gov/grants/guide/notice-files/NOT-AI-16-026.html>.

CDC established the U.S. Zika Pregnancy Registry and is collaborating with state, tribal, local, and territorial health departments to collect information about pregnancy and infant outcomes following laboratory evidence of Zika virus infection during pregnancy. Pregnant women in Puerto Rico with laboratory evidence of Zika virus infection, with or without symptoms, are eligible for the Puerto Rico Zika Active Pregnancy Surveillance System. The data collected through these registries will be used to update recommendations for clinical care, to plan for services for pregnant women and families affected by Zika virus, and to improve prevention of Zika virus infection during pregnancy.

CDC's research on birth defects associated with Zika also includes collaborating with the Brazil Ministry of Health to assess an association between Zika virus infection and a reported increase in microcephaly cases. CDC worked with the Colombia Ministry of Health to establish a cohort of approximately 1,000 pregnant women with symptomatic confirmed or suspected Zika virus infection during their pregnancy. The study is evaluating the relationship between Zika virus infection during pregnancy and a spectrum of adverse pregnancy, birth, and fetal/neonatal outcomes and estimate the risk of each outcome among women with confirmed or suspected Zika virus infection. Through its offices in Guatemala, CDC is adding Zika virus testing to an ongoing CDC-sponsored study in Panama and El Salvador that is examining the relationships between birth outcomes and influenza in a cohort of pregnant women. CDC anticipates preliminary results by August 2016.

d. The link between Zika virus infection and Guillain-Barré syndrome or other side effects in infected individuals:

Guillain-Barré syndrome (GBS) is considered an autoimmune polyneuropathy meaning the immune system mistakenly damages nerves throughout the body leading to muscle weakness and possibly paralysis. Although GBS is uncommon, when people do develop the disease, it is often after viral and bacterial infections or very rarely immunizations. Most people with GBS will recover within weeks or months, and prior NINDS-funded trials showed that plasmapheresis and intravenous gamma globulin infusions hasten the recovery from GBS. Zika has been linked to GBS, but the incidence of GBS among Zika infected individuals appears to be low. The molecular and cellular mechanisms by which Zika might cause GBS are not clear. Within NIH, ongoing NINDS-funded research on GBS is investigating whether antibodies that bind to molecules on nerves are present in individuals after Zika infection and how this may lead to neuropathy. NINDS researchers are developing animal and cell models of Zika infection that will allow a deeper understanding of the pathophysiology of Zika-associated GBS. To facilitate research on Zika and GBS, NINDS coordinated a teleconference involving the NIH Zika coordinating group and GBS researchers. Additionally, NINDS has issued a notice to clarify NIH's interest in supporting research on GBS and other neurological consequences of Zika infection. This notice may be accessed by going to <https://grants.nih.gov/grants/guide/notice-files/NOT-NS-16-027.html>.

6. Currently, States may use some of the grant money they receive from the CDC through the Epidemiology and Laboratory Capacity (ELC) grant program for vector control activities.

a. What types of vector control methods can States employ when using ELC grant funds?

CDC provides financial and technical resources to states and territories through our ELC cooperative agreements to strengthen their capacity to prepare for and respond to emerging threats like Zika virus. As outlined in the April 2016 ELC guidance, states, local jurisdictions, and territories may use ELC resources to implement vector control and surveillance activities, as well as community education and prevention programs to reduce human-mosquito contact and therefore reduce the risk of Zika transmission. Vector control strategies can include vector surveillance, mapping, insecticide resistance, integrated pest management, larviciding and adulticiding. Effective implementation of vector control measures will require trained staff.

b. What restrictions does the Department or its components place on the use of these funds for vector control?

Vector control strategies can include vector surveillance, mapping, insecticide resistance, integrated pest management, larviciding, and adulticiding.

c. Does the Department administer any other grant programs, at present, providing funding to States for vector control?

CDC provides financial and technical resources to states, local jurisdictions, and territories through our ELC and Public Health Emergency Preparedness (PHEP) cooperative agreements to strengthen their capacity to prepare for and respond to emerging threats like Zika virus. Historically, vector control has been a state and local responsibility. States use AI cooperative agreement funding to support planning, but vector control implementation is not within scope of the PHEP cooperative agreement. The PHEP cooperative agreement provides funding to assist public health departments in emergency planning and preparedness activities. The PHEP resources may be used to help health departments expand their capacity to prepare for cases of local Zika virus transmission in their areas. CDC guidance allows PHEP awardees to use PHEP funds to provide public health emergency management and response support for potential Zika virus outbreaks in their jurisdictions. This includes Zika response planning, program management, and support activities including but not limited to emergency response coordination, community outreach, risk communications, coordinating response operations such as supporting the infrastructure needed to implement vector control, and outreach and training which target clinicians and other healthcare providers.

7. How is your Department coordinating with the U.S. Department of Agriculture (USDA) on vector control research to close any gaps and prevent unnecessary duplication?

In collaboration with DOD, USDA, the Department of Homeland Security, and the Environmental Protection Agency, HHS is working to accelerate vector control research and to coordinate response efforts in the Commonwealth of Puerto Rico, the U.S. Virgin Islands, and American Samoa. HHS is also working with these and state partners to coordinate vector preparedness efforts across the United States in areas with known populations of the mosquitoes that transmit Zika virus.

8. Can States utilize funds received through Public Health Emergency Preparedness grants or the Hospital Preparedness Program grants to respond to the Zika virus? If so, what conditions are placed upon the use of those funds?

PHEP funding is governed by a number of statutory requirements and is intended to primarily support all-hazards preparedness. However, CDC is providing as much flexibility as possible to awardees as they adjust their fiscal year 2016 plans to account for Zika. In February 2016, CDC issued guidelines to PHEP awardees on Zika preparedness and response activities that can be supported with the \$145 million in PHEP supplemental funding for Ebola and other infectious diseases. Additionally, as announced on July 1, \$25 million in PHEP resources have been

provided to 53 state, territorial and local health departments to specifically address Zika. This funding is intended to ensure state, local, and territorial operational readiness for Zika virus disease by addressing planning and operational response gaps for Zika.

In addition, the Hospital Preparedness Program (HPP) provides resources to states, territories, and eligible municipalities to enhance surge capacity and improve health care preparedness for emergencies that exceed the day-to-day capacity of the health and emergency response systems. Funding is used to specifically support regional health care coalition (HCC) development and planning. HCCs incentivize diverse and often competitive health care organizations, such as hospitals, long-term care facilities, and EMS, with differing priorities and objectives to work together. HCCs collaborate to ensure that each member has the necessary medical equipment and supplies, real-time information, communication systems, and trained health care personnel to respond to an emergency. These regional efforts help each patient receive the right care at the right place at the right time regardless of the type of emergency, including potential outbreaks of infectious diseases such as Zika. At this time, HHS has not received any requests from HPP awardees to use their annual cooperative agreement funding for activities outside the currently approved scope of work. Requests to undertake considerable planning and preparation for Zika using annual HPP awards will need to be approved by grants management and the HHS program office prior to using funds for such purposes.

9. Please provide a description of any other currently available Department resource that States and localities can use immediately to combat the Zika virus.

HHS recognizes this is a very difficult and challenging issue for state, local, and territorial public health departments. In early April, CDC hosted more than 30 states and U.S. territories in Atlanta to help jurisdictions refine risk-based, Zika preparedness and response plans in advance of the warmer weather and start of mosquito season. To prepare the nation's health care systems to proactively respond to the Zika virus, ASPR's HPP is providing assistance and planning resources to awardees and health care coalitions. HPP has allowed the use of existing annual HPP funds to prepare for suspected or known Zika patients. This funding allows health care coalitions and their members to coordinate, share information, educate, exercise, and train for Zika. In addition to funding, ASPR's Technical Resources Assistance Center & Information Exchange (TRACIE) is providing Zika-specific technical assistance and planning resources to help awardees, health care coalitions, and individual providers to assess their readiness for Zika, and to fill existing gaps.

In April 2016, the Administration identified \$374 million of existing HHS resources to finance immediate Zika response activities such as mosquito control, laboratory capacity, development of diagnostics and vaccines, supporting pregnant mothers and babies, tracking and mapping the spread and effects of Zika in humans, and other prevention and response efforts in the continental United States, Puerto Rico, and other U.S. Territories.

These reallocated funds are being used to provide support to state and local entities. However, these funds are not enough to support an ongoing comprehensive Zika response and can only temporarily address what is needed until Congress acts on the Administration's emergency supplemental request. With this available funding, on July 22, CDC awarded more than \$60

million in Epidemiology and Laboratory Capacity grant funding to states and territories to address Zika by improving mosquito control and monitoring, building laboratory capacity, and enhancing epidemiological surveillance and investigation. On August 2, CDC also awarded more than \$16 million to 40 states and territories to establish, enhance, and maintain information-gathering systems to rapidly detect microcephaly. Additionally, as mentioned previously CDC encourages PHEP awardees to address Zika with their PHEP funding, and CDC has provided \$25 million in PHEP resources specifically for Zika.

Emergency supplemental funding continues to be urgently needed to support the full range of activities needed to prevent, detect, and respond to further transmission of the Zika virus.

10. How is the Department coordinating with the Department of Defense to conduct research and development of MCMs for the Zika virus?

There is collaboration between HHS (ASPR/BARDA, NIH/NIAID) and DOD/WRAIR to make and test an inactivated whole virion vaccine. Preclinical testing of the vaccine candidate has begun with human clinical studies, supported by NIH/NIAID and WRAIR, to start in the fall. BARDA anticipates transferring the WRAIR vaccine candidate to one of the BARDA CIADMs for process optimization and larger scale manufacturing. This vaccine candidate will also be eligible for out-licensure to industry partners and some discussions with potential partners have already begun.

Coordination with DOD on policy and strategic issues occurs through the Zika Medical Countermeasures Senior Steering Group chaired by the ASPR and with the agencies that are regularly represented on the PHEMCE and subsequently through the interagency process led by the White House National Security Council.

11. To what extent is Health and Human Services working with the Department of the Interior and USDA to understand (1) the role animals, including wildlife, companion, and food animals could play in the amplification and spread of the disease and (2) any efforts the departments may have underway to control diseases of this nature?

CDC is currently engaged in discussions with the Department of Interior's National Wildlife Health Center about possibly working together on non-human primate testing in Zika-affected areas.

CDC is aware of one report on the first detection of Zika virus in primates in Brazil. Researchers tested samples (sera and oral swabs) from fifteen marmosets and nine capuchin-monkeys captured from July to November of 2015 in Ceará State, an epidemic area for Zika. Seven (29%) of 24 primates tested were positive for Zika virus by PCR. The strain of Zika was sequenced and reported to have 100% similarity to other Zika viruses found in South America. Animals that were sampled cohabitated with people or were pets. This study raises concerns that non-human primates could be possible reservoirs for Zika virus and further studies are needed.